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Abstract: Atrial fibrillation (AF) is the clinically most prevalent rhythm disorder with large impact on quality of life and increased risk for hospitalizations and mortality in both men and women. In recent years, knowledge regarding epidemiology, risk factors, and patho-physiological mechanisms of AF has greatly increased. Sex differences have been identified in the prevalence, clinical presentation, associated comorbidities, and therapy outcomes of AF. Although it is known that age-related prevalence of AF is lower in women than in men, women have worse and often atypical symptoms and worse quality of life as well as a higher risk for adverse events such as stroke and death associated with AF. In this review, we evaluate what is known about sex differences in AF mechanisms-covering structural, electrophysiological, and hormonal factors-and underscore areas of knowledge gaps for future studies. Increasing our understanding of mechanisms accounting for these sex differences in AF is important both for prognostic purposes and the optimization of (targeted, mechanism-based, and sex-specific) therapeutic approaches.

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Mechanisms of sex differences in atrial fibrillation: role of hormones and differences in electrophysiology, structure, function, and remodelling

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Atrial fibrillation (AF) is the clinically most prevalent rhythm disorder with large impact on quality of life and increased risk for hospitalizations and mortality in both men and women. In recent years, knowledge regarding epidemiology, risk factors, and patho-physiological mechanisms of AF has greatly increased. Sex differences have been identified in the prevalence, clinical presentation, associated comorbidities, and therapy outcomes of AF. Although it is known that age-related prevalence of AF is lower in women than in men, women have worse and often atypical symptoms and worse quality of life as well as a higher risk for adverse events such as stroke and death associated with AF. In this review, we evaluate what is known about sex differences in AF mechanisms—covering structural, electrophysiological, and hormonal factors—and underscore areas of knowledge gaps for future studies. Increasing our understanding of mechanisms accounting for these sex differences in AF is important both for prognostic purposes and the optimization of (targeted, mechanism-based, and sex-specific) therapeutic approaches.

Keywords

Atrial fibrillation • Sex differences • Mechanisms • Electrophysiology • Structural remodelling • Sex hormones • Estrogen

Introduction

Atrial fibrillation (AF) is the clinically most prevalent rhythm disorder with large impact on quality of life and increased risk for hospitalizations and mortality in both men and women.^{1,2} In recent years, knowledge regarding epidemiology, risk factors, and patho-physiological mechanisms of AF has greatly increased.³ Sex differences have

been identified in the prevalence, clinical presentation, associated comorbidities, and therapy outcomes of AF.^{4–8} Although it is known that age-related prevalence of AF is lower in women than in men,⁹ women have worse and often atypical symptoms and worse quality of life as well as a higher risk for adverse events such as stroke and death associated with AF.^{10,11} This is also reflected in the current AF risk algorithms such as the

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Table 1 Sex differences in prevailing mechanisms/diseases predisposing to atrial fibrillation

	Men	Women
Prevailing risk factors/diseases predisposing to AF	Coronary heart disease and cardiovascular risk factors Excessive sports (vagal AF) High BMI/metabolic disease (increased epicardial fat)	Heart failure, particularly diastolic heart failure (HFpEF) Hypertension and left ventricular hypertrophy Valvular heart disease High BMI/metabolic disease/epicardial fat
	Potential pro-arrhythmic mechanisms increasing AF prevalence in men	Potential anti-arrhythmic mechanisms reducing AF prevalence in premenopausal women
Hormonal effects impacting on AF prevalence	Detrimental testosterone effects on atherosclerosis/CAD Pro-arrhythmic testosterone effects on atrial electrical features (shorter APD facilitating re-entry) More pronounced fibrotic remodelling in male animals (testosterone-effect?)	Beneficial oestrogen-effects on cardiovascular risk factors Anti-arrhythmic oestrogen-effects on atrial electrical features (longer atrial APD) Beneficial oestrogen-effects on structural remodelling (attenuation of fibrosis) Beneficial oestrogen-effects on diastolic function Reduction of epicardial fat (by oestrogen? indirect evidence: more epicardial fat in post-menopausal women)

AF, atrial fibrillation; APD, action potential duration; BMI, body mass index; CAD, coronary artery disease; HFpEF, heart failure with preserved ejection fraction.

CHA₂DS₂VASc score.³ Despite the advances in the treatment of AF, women are more prone to AF recurrences compared to men.^{6,11} While the exact mechanism for these sex differences remains to be elucidated, the importance of structural, electrophysiological, and hormonal factors have been proposed.⁶ Data regarding sex differences in the mechanisms of AF are scarce, and a better understanding is important both for prognostic purposes and the optimization of therapeutic approaches.

Based on a thorough electronic literature search conducted using PubMed, this review evaluates what is known about sex differences in AF mechanisms and underscores areas of knowledge gaps for future studies.

Epidemiology: sex differences in atrial fibrillation prevalence, age of onset, clinical presentation, and co-morbidities

Atrial fibrillation is more common in men (0.06%) than in women (0.04%).¹² In observational studies in Western countries, women have 30–50% lower age-adjusted incidence and prevalence of AF, indicating that the substrate for AF develops less readily in women. In East/Asian countries, overall AF prevalence is lower than in Western countries for which reports regarding sex distribution have been less consistent varying from equal to lower prevalence in women than in men.¹³ In general, AF incidence increases with age for both sexes. Given the higher life expectancy of women, the absolute numbers and lifetime risk (~23%) for AF are similar in both sexes.¹⁴ The prevailing mechanisms predisposing to AF, however, differ between men and women (Table 1), as highlighted in the following chapters.

Women are more likely to present with persistent AF and atypical symptoms (weakness and fatigue) and to report a worse quality of life than men.⁵ Although asymptomatic AF is less common among women,¹⁵ atypical symptoms may delay diagnosis and therapy and may contribute to the worse outcomes seen in women.¹⁶

Sex differences in atrial fibrillation subtypes

Idiopathic atrial fibrillation and genetic atrial fibrillation

Genetic predisposition has been attributed to individuals with familial aggregation of early-onset idiopathic AF, but data on sex-specific differences in idiopathic AF have been controversial.¹⁷ Mothers of patients with AF or atrial flutter and women with ≥2 affected siblings have higher AF risk than their male counterparts.¹⁸ Similarly, a small study observed that more women had familial idiopathic AF.¹⁹ This is in contrast to a large registry, which showed that men with a 1st degree relative with idiopathic AF have 37% higher AF risk than women.²⁰ The genetic basis of these differences is not known, but X-linked variants of the protective *KCNK5* gene and a deletion in the *EMD* gene have been proposed as contributing factors.^{21,22}

Exercise-associated atrial fibrillation and autonomic atrial fibrillation

Pronounced sex differences exist in the connection between exercise and AF: moderate exercise reduces the risk of AF in women (−8.6%), and intense exercise is able to reduce AF risk in women even more by 30%. In male patients, moderate exercise also reduces AF risk. Strong exercise, however, increases the risk for AF in men, pointing towards a U-shape relation in men.^{23–27} Excessive endurance sports (e.g. more than 1500 h of sports/year) increases the risk of AF three times in men. These patients also have higher recurrence rates after pulmonary vein isolation (PVI).^{28–30}

Male athletes show more marked concentric ventricular and atrial remodelling with altered diastolic function, which associates with a higher blood pressure during exercise as well as a higher sympathetic tone compared to female athletes.³¹ This atrial remodelling might be a reason for the higher rate of AF in sportsmen.³¹ In addition, studies in rat models revealed that long-term endurance exercise causes a combination of structural remodelling and (central and end-organ) vagal enhancement,³² which may further promote re-entry by causing spatially heterogeneous shortening of atrial refractoriness.³³ Indeed, despite the observation of an overall higher sympathetic tone during exercise,³¹ in (male) athletes, paroxysmal AF occurs three times more often in situations of high vagal tone (such as rest, sleep, or postprandial) than in non-athletes.³⁴ In line with these observations, a low heart rate has generally been associated with an increased risk for AF.³⁵

While in young male athletes, these vagal triggers predominate; in post-menopausal women an increased predominant sympathetic tone is observed.^{36,37} This increased sympathetic/parasympathetic balance has generally been associated with a high risk of AF³⁵ and is particularly often associated with AF in organic heart disease and post-cardiac surgeries.³⁸

Co-morbidity-associated atrial fibrillation

Women often develop AF at an older age than men.³⁹ In the Framingham Heart Study, for example, 74% of women with AF were aged ≥ 70 years compared to only 58% of men, strongly suggesting that more comorbidity may be present and possibly causative in women with AF¹ (Table 1).

All classic cardiovascular risk factors, except for diabetes, are predictive of AF in both sexes. High body mass index (BMI) has been shown to be the strongest predictor for AF with a higher hazard ratio in men than in women. Moderate alcohol intake increases the risk for AF only in men, while high alcohol intake is associated with a heightened AF risk in both sexes.^{40,41} No sex-specific differences have been consistently demonstrated for other risk factors such as hyperthyroidism.^{25,39,41–43}

Several comorbidities, however, are differently associated with AF in men and women: women with heart failure have a 14-fold risk and men a 8.5-fold risk of developing AF.⁴⁴ In addition, AF is an independent risk factor for new onset heart failure with preserved ejection fraction (HFpEF) in women but not in men.⁴⁵ Although over the past 50 years the prevalence of valvular heart disease has generally decreased in women with AF in high income countries, there is still a higher prevalence of valvular heart disease and hypertension and lower prevalence of coronary heart disease in women than in men with AF.^{1,8,46}

Sex hormone effects on atrial fibrillation

Atrial fibrillation in menopausal and post-menopausal women

The incidence of AF in premenopausal women is low but the incidence increases after menopause particularly at ages over 50 years, suggesting a beneficial effect of oestrogen and/or a harmful effect of post-menopausal hormonal changes—such as the pronounced decrease in oestrogen—with regards to the development of AF.¹³ With the decrease of oestrogen levels during menopause, blood

pressure, low-density lipoprotein cholesterol, metabolic syndrome, and BMI increase. All these effects are well-established risk factors for developing AF⁴⁷ and their increase after menopause may explain the partial catch up in the incidence of AF in post-menopausal women (Table 1).

In line with these observations, there is evidence for a higher incidence of AF in patients undergoing anti-oestrogen treatment and for a lower risk of AF with (oestrogen-based) hormonal replacement therapy, albeit published data are conflicting.^{48–50} While oestradiol was shown to reduce the risk for AF,⁵¹ conjugated oestrogens alone have been reported to increase AF risk (two-fold compared to oestradiol)^{51,52} and combined oestrogen-progesterone based hormonal replacement therapy had either no effect⁵² or decreased AF incidence,⁴⁹ suggesting a complex interaction and an impact of the hormonal preparation and its oestrogen-receptor specificity.

Atrial fibrillation during pregnancy and postpartum

Observational studies suggest that pregnancy may exacerbate supra-ventricular tachycardias in general.⁵³ Prevalence of AF in pregnant women, however, is very low (0.05%)⁵⁴ and is generally limited to patients with structural heart disease, in which AF incidence is a little higher (1.3%).⁵⁵ Nevertheless, several electrical and electro-mechanical changes have been observed during pregnancy such as an increase in P wave duration and dispersion and in atrial electro-mechanical coupling interval measured by tissue doppler⁵⁶ that are well-known markers for increased AF incidence in normal hearts. As these observations were made in patients with pre-eclampsia, however, it is unclear whether these are alterations normally occurring during pregnancy or being simply associated with the vascular/atrial susceptibility of an abnormal pregnancy. Atrial fibrillation during the peripartum period may occur mainly due to drug therapy such as terbutaline during tocolysis^{57,58} and also as an expression of peripartum cardiomyopathy.⁵⁹

Atrial fibrillation and testosterone

The epidemiological data on the link between AF and testosterone are conflicting. Data from the Framingham study show an association between AF incidence and reduced total testosterone levels in men aged 55 years and above, with the strongest association seen in men ≥ 80 years of age, with a 3.5-fold increase in AF risk for every standard deviation reduction in testosterone levels.⁶⁰ Similarly, a smaller cross-sectional study demonstrated a similar association between reduced testosterone levels and lone AF.⁶¹ In contrast, the Multi-Ethnic Study of Atherosclerosis study showed that higher levels of endogenous bioavailable testosterone seemed to contribute to AF development.⁶² The differences in findings may in part be due to methodological differences in measuring testosterone (total vs. bio-available testosterone) but may also relate to competing mechanisms of direct and indirect testosterone effects.

The data on the effects of testosterone replacement are equally conflicting. In a recent study on >76 000 individuals, normalization of testosterone levels with replacement therapy was associated with a decreased incidence of AF.⁶³ However, preclinical studies have shown the opposite effect, with testosterone replacement increasing arrhythmogenesis in pulmonary veins (PVs) and the left atrium, probably by enhancing adrenergic activity.⁶⁴

Mechanisms underlying sex differences in atrial fibrillation

Sex differences in electrophysiological properties of atria

Sex differences in electrophysiology and calcium handling

Experimental models show sex differences in the electrophysiology of the left atrium. In male mice, PVs have a higher spontaneous beating rate, increased burst firing and more delayed afterdepolarizations (57% vs. 16%).⁶⁵ Additionally, male mice have slower sino-atrial impulse-generation activity. Thus, spontaneously higher PV beating rates can compete with sino-atrial activity leading to arrhythmias. Sex differences in arrhythmogenesis can also be explained by differences in calcium and sodium channel regulation.⁶⁶ Mouse studies have shown that late sodium current, calcium transients, and sarcoplasmic reticulum calcium contents of the posterior wall of the left atrium were greater in male cardiomyocytes than in females, which may contribute to increased ectopic activity.⁶⁶ Interestingly, no differences were found in the right atrium.

In contrast, a clinical study in women undergoing AV nodal reentry tachycardia ablation showed shorter atrial effective refractory period (AERP) in women rather than longer.⁶⁷ In a small cohort of patients that underwent AF ablation,⁶⁸ these sex differences in AERP were not confirmed, likely due to some electrical (and structural) remodelling present in these patients with paroxysmal AF. This small study suggested that the prevalence of non-PVI triggers was significantly more frequent in women than in men (16% vs. 8.4%).

Sex hormone effects on electrophysiology and calcium handling

Cardiac myocytes express oestrogen and androgen receptors, strongly suggesting that sex hormones may directly affect ion channels and their expression.^{69,70}

Most research has focused on sex hormone effects on ion channels/currents expressed in atria and ventricles. Testosterone increases repolarizing I_{Kr} , I_{K1} , and I_{Ks} ,^{71,72} and acutely reduces $I_{Ca,L}$.⁷³ Oestrogen exerts complex effects on I_{Kr} : it blocks I_{Kr} directly⁷⁵ but may also increase I_{Kr} by promoting HERG trafficking.⁷⁶ In addition, oestrogen reduces I_{Ks} by reducing its beta-subunit KCNE1,⁷⁷ reduces I_{to} ,⁷⁸ and increases $I_{Ca,L}$.⁷⁹ These alterations of ion currents result in a net oestrogen-induced prolongation of action potential duration (APD) and QT interval and a net testosterone-induced shortening of APD/QT (Figure 1).⁸⁰ The shortened APD in male atria may be pro-arrhythmic by facilitating re-entry, while the longer APD in female atria may exert anti-arrhythmic effects relating to AF (contrasting with its pro-arrhythmic effects in the ventricles). As most studies on hormone effects on ion currents were performed in ventricular cardiomyocytes, the transferability to the atrial electrical phenotype needs confirmation.

Only few data are available on sex hormone effects on 'atrial' ion channels/currents and most were derived from non-cardiac tissue also expressing these channels. During pregnancy (with high oestrogen levels), I_f current densities and automaticity are increased in mice.⁸¹ Oestrogen upregulates Ca^{2+} -activated small conductance potassium channels (SK3) in colonic smooth muscle cells⁸² and downregulates two-pore domain K^+ channels (TASK-1) in neural

cells (Figure 1).⁸³ A likewise oestrogen-induced reduction of TASK-1 in the atria would prolong the atrial APD and exert pro-arrhythmic effects, as demonstrated in patients with lone AF harbouring loss-of-function mutations in KCNK3/TASK-1.⁸⁴ As SK expression has been demonstrated to be particularly high in the PVs (as compared to the rest of the atria),⁸⁵ oestrogen-induced changes in SK expression might modulate triggered activity from the PVs. Whether similar oestrogen-effects are indeed observed in the atria, however, needs to be assessed.

Sex hormone effects on calcium handling properties can also contribute to atrial arrhythmogenesis: oestrogen increases the propensity for triggered activity by increasing $I_{Ca,L}$,⁷⁹ NCX activity,⁸⁶ and RyR2 leakiness.⁸⁷ Testosterone in contrast reduces triggered activity by increasing SERCA activity,^{79,88} and decreasing $I_{Ca,L}$ (Figure 1).⁷³ In line with these findings, testosterone deficiency facilitates atrial arrhythmia by reducing binding of FKBP12.6 to RyR2 resulting in increased calcium leakage.⁸⁹

Sex differences in electrical remodelling

There is little direct evidence on whether sex differences in atrial electrical remodelling play a role in sex differences in AF risk. Biochemical and histological analysis of atrial tissue obtained during cardiac surgery showed that remodelling-induced changes of connexins and collagen in AF are broadly similar between men and women, though women exhibited somewhat stronger AF-induced increase in Cx40.⁹⁰ Indirect evidence indicating that sex may be an important determinant of the degree of electrical remodelling in the left atrium comes from a study on heart failure patients. Analysis of mRNA expression of genes encoding for ion channel subunits important in cardiac conduction and arrhythmogenesis in left atria of explanted human hearts showed differential remodelling between sexes, with lower expression levels in transcripts encoding for K(v)4.3, KChIP2, K(v)1.5, and K(ir)3.1 in the failing female left atrium as compared with the male left atrium.⁹¹ Differential electrical remodelling between sexes was also seen in a study in rabbits on left ventricular (LV) hypertrophy with less pronounced APD prolongation in left ventricles in females than in males leading to longer APD in males than females—thus reversing the sex differences observed at baseline.⁹² Whether similar sex differences in remodelling also occur in the atria remains to be investigated.

Sex differences in structure and function of atria

Sex differences in atrial anatomy, structure, and function

Morphological, structural, and functional sex differences in the atria have been described in association with AF. Healthy women have smaller maximal left atrial volumes (89 ± 21 mL vs. 103 ± 30 mL), smaller left atrial anteroposterior diameter, and lower left atrial stroke volumes (48 ± 15 mL vs. 58 ± 23 mL).^{93,94} In addition, magnetic resonance imaging (MRI) analyses revealed sex differences in atrial mechanical function in healthy subjects, e.g. in atrial conduit and booster pump function.^{95,96} In contrast to the observations in healthy subjects, women referred for AF ablation usually have larger atria than men,⁹⁷ which may be partly due to the facts that these women were older, had a longer AF history, more hypertension, and more valve disease than the men in the study.

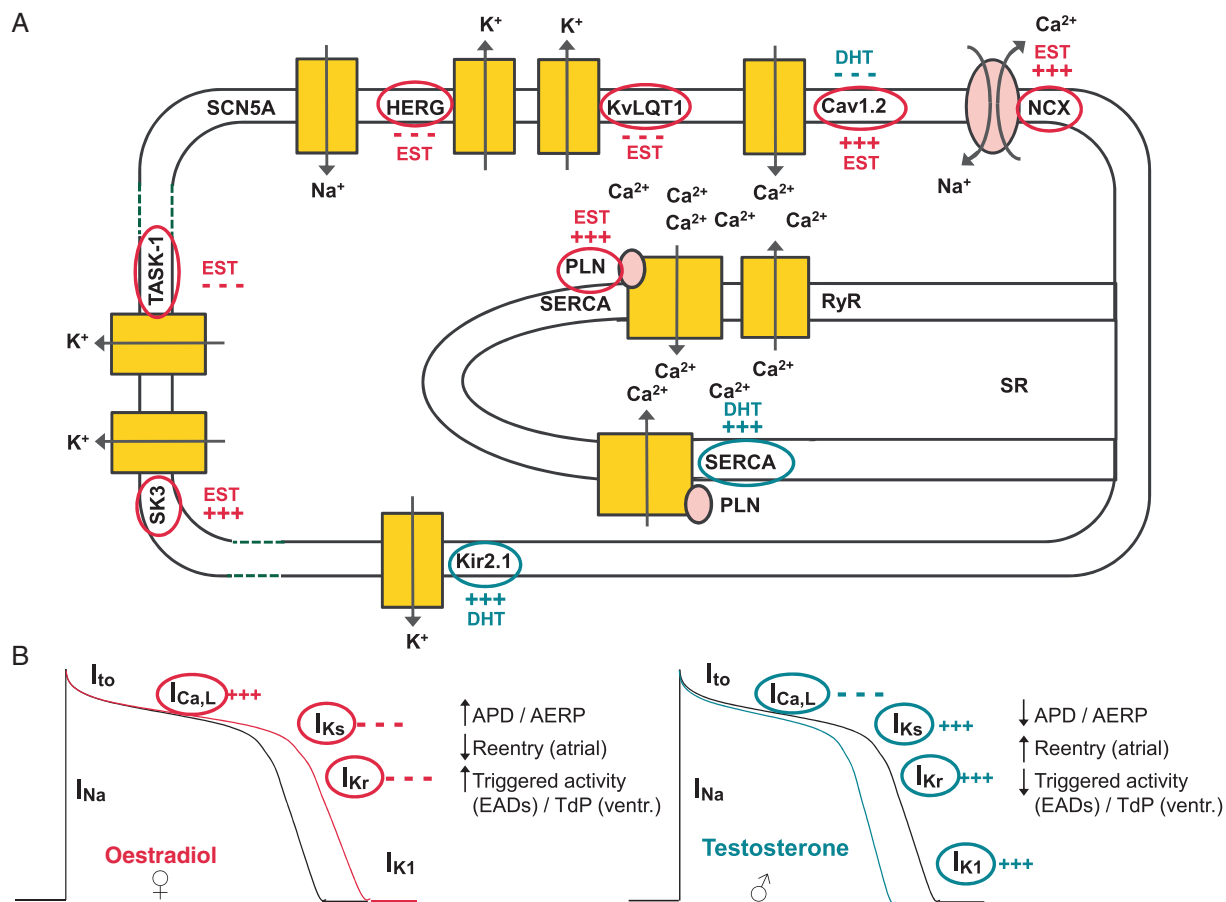


Figure 1 (A) Schematic figure indicating sex hormone effects on cardiac ion channels/currents and calcium handling proteins in cardiomyocytes. Effects on ion channels that have thus far only been demonstrated in non-cardiac tissues are indicated in the left corner separated by green dotted lines. Oestrogen-induced changes are colour-coded in red, testosterone-induced changes in turquoise. (B) Illustration of resulting effects on cardiac repolarization and arrhythmogenic mechanisms. --, reduction; + + +, increase; ↑, increase/prolongation, ↓, decrease/abbreviation. AERP, atrial effective refractory period; APD, action potential duration; DHT, testosterone; EAD, early afterdepolarization; eNOS, endothelial nitric oxide synthase; EST, oestrogen; IL, interleukin; PAI 1, plasminogen-activator inhibitor 1; SR, sarcoplasmic reticulum; TdP, Torsade-de-Pointes; HERG/*I_{Kr}*, alpha-subunit to repolarizing delayed rectifier potassium current *I_{Kr}*; KvLQT1/*I_{Ks}*, alpha-subunit to repolarizing slow delayed rectifier potassium current *I_{Ks}*; Kir2.1/*I_{K1}*; SCN5A/*I_{Na}*, alpha-subunit to depolarizing sodium current *I_{Na}*; Cav2.1/*I_{Ca,L}*, alpha-subunit to L-type calcium current *I_{Ca,L}*; SK3, small-conductance calcium-activated potassium channel; TASK-1, two-pore domain potassium channel; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

Tissue fibrosis plays a major role in the development of AF and its progression to a persistent/permanent status. Sex differences regarding the degree of fibrosis in the different clinical variants of AF were demonstrated by histopathological studies and with MRI.⁹⁸ It is not clear, whether these sex differences in the extent of fibrosis with more pronounced fibrosis in women are mainly due to inherent differential expression of fibrosis-related genes and proteins or due to the age of men and women with AF (younger age in men with AF).⁹⁰

A study looking at PV sleeves from patients with and without longstanding persistent AF demonstrated increased fibrosis in females with AF.⁹⁰ These sex differences in fibrosis remodelling in longstanding persistent AF were mainly due to the inherent differential expression of fibrosis-related genes and proteins, with those related to the TGFβ/Smad3 pathway being up-regulated in females, suggesting sex-specific aggravation of fibrosis remodelling. There is also evidence to suggest that this more extensive left atrial structural remodelling leads

to greater deterioration in left atrial appendage function in women with high calculated risk of stroke in AF compared with men.⁹⁹

Sex hormone effects on atrial mechanical function

Data on sex hormone effects on atrial function were obtained in animal studies. In rats, androgens produce acute vasodilation, increase contractility, and increase the sino-atrial recovery time by depressing spontaneous depolarization involved in atrial pacemaking.¹⁰⁰ Androgens cause a larger response to inotropes in male atria via a post-synaptic increase in intracellular cAMP and independently of beta1-adrenoceptors.¹⁰¹ In female mice though, oestrogens are those that drive the sensitivity to catecholamine by down-regulating the beta1-receptors, depending on the oestrous cycle.¹⁰² In female sheep, in contrast, oestrogen causes LV enlargement and increased stroke volume.¹⁰³

Sex hormones also modify the response to volume overload and the secretion of atrial natriuretic peptide (ANP) as demonstrated in

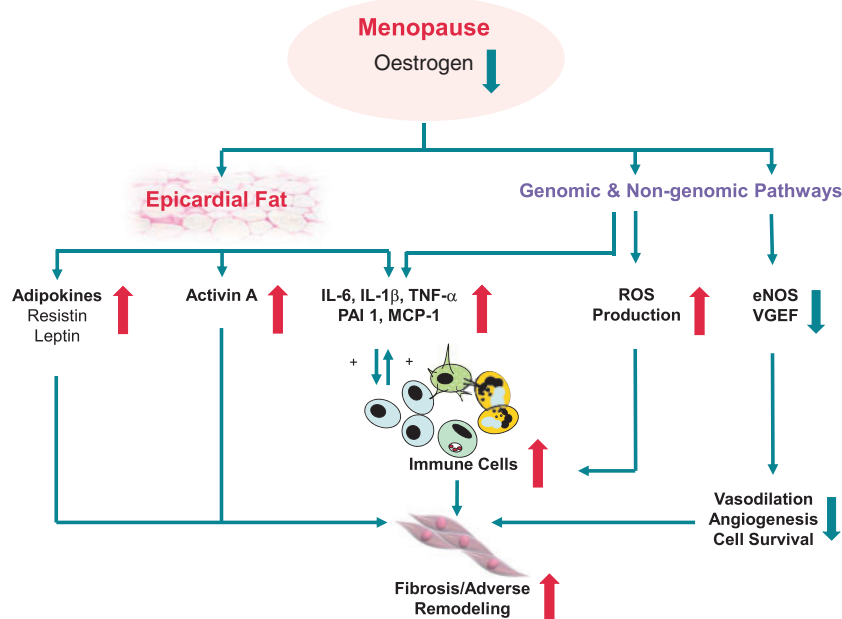


Figure 2 Schematic figure indicating effects of menopause-associated reduction in oestrogen on epicardial fat and related (pro-inflammatory) signalling pathways and fibrotic remodelling mechanisms. ↑, increase/activation, ↓, decrease; MCP-1, monocyte chemoattractant protein-1; ROS, reactive oxygen species.

studies in rats. Oestrogen increases the basal secretion but does not influence the stretch-induced ANP secretion. In contrast, although testosterone does not affect basal secretion, it completely abolishes the stretch-induced increase in ANP secretion.¹⁰⁴

Sex differences in structural remodelling of the heart the atria

Animal data suggest sex-specific differences in pathological remodelling. In mouse models of myocarditis as well as in models of isoproterenol-induced heart failure, fibrotic responses are generally more prominent in male mice, showing higher numbers of TLR4⁺ CD11b⁺ monocytes, neutrophils, mast cells, and dendritic cells, and increased Th1 helper cell responses compared to females.¹⁰⁵ In contrast, protective Th2 responses, increased B cells, more inhibitory Tim-3⁺ CD4⁺ T cells, and more T regulatory cells dominate the picture in female animals.^{105,106} Consistent with these findings, intracardiac macrophages from male mice preferentially expressed iNOS, IL-12, TNF- α , and CD16/32, markers associated with M1 activation,^{107,108} while heart-infiltrating macrophages in females showed a M2 activation pattern including arginase 1, IL-10, and M ϕ -MR expression.

Fibrosis is an event that affects the atria as well as the ventricles, and several lines of evidence suggest that oestrogens indeed play an important role in attenuating this process of adverse remodelling. Thus, it is not surprising that expression of fibrosis-related genes, mainly those related to the TGF β /Smad3 pathway, is up-regulated in post-menopausal women with AF (Figure 2).¹⁰⁰ Nevertheless, the exact mechanisms through which sex modulates structural atrial remodelling still remain to be identified.¹⁰⁹

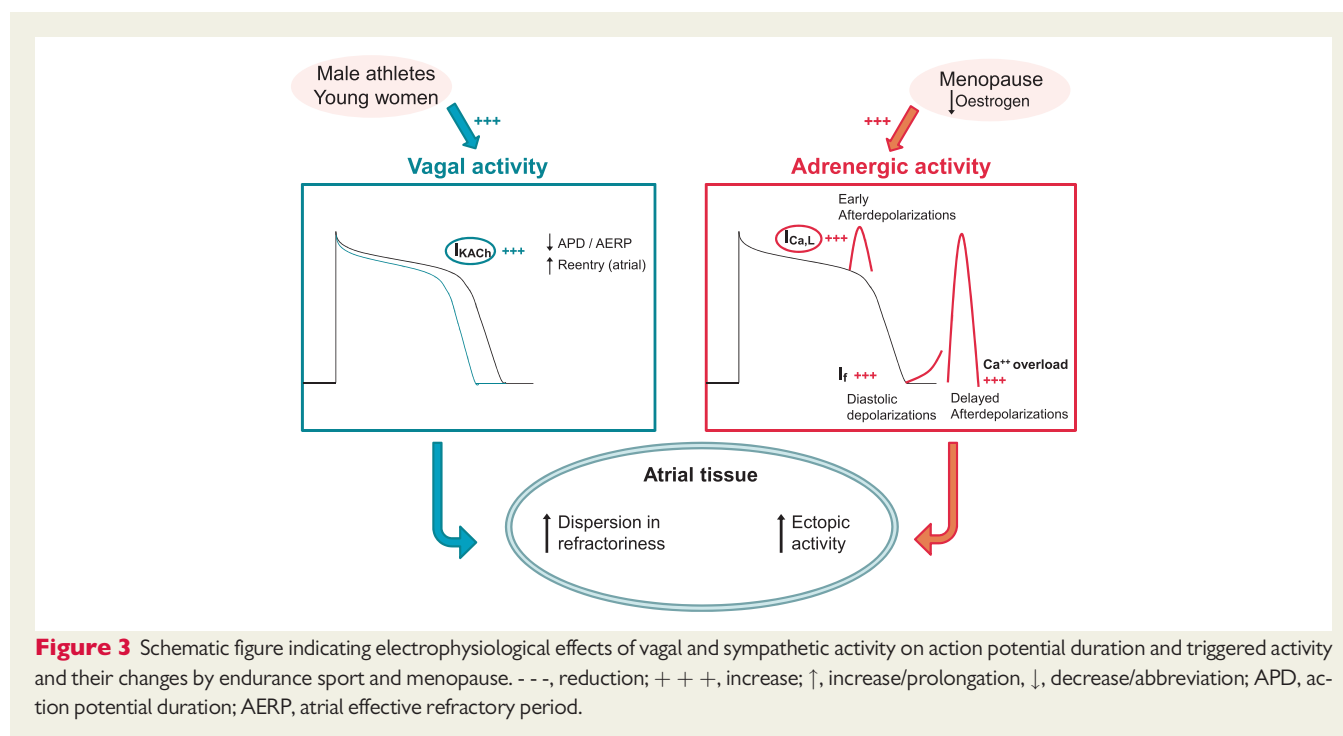
Sex differences in cardiac autonomic modulation and neuro-humoral responses

Sex differences in cardiac autonomic activity

The autonomic nervous system (ANS) including the sympathetic and parasympathetic system and the intrinsic neuronal network—and its alterations—plays an important role in the pathogenesis of AF.^{110–112} Both parts of the ANS are involved in the initiation and maintenance of AF. The role of the parasympathetic system in AF is mainly attributed to the shortening in APD and increased dispersion of refractoriness in the atrial myocardium facilitating initiation and maintenance of AF.³³ Vagal activation exerts these effects mostly via acetylcholine activated K⁺ channels.¹¹³ Sympathetic stimulation can also promote AF by increasing Ca²⁺ release; thereby causing afterdepolarization formation as a trigger for AF (Figure 3).

When compared to men of the same age, women seem to have more dominant vagal tone indexed by measures of heart rate variability,^{114,115} although this sex difference disappears with aging (and consecutive changes in hormones).¹¹⁶

Sex hormones influence the autonomic tone. As the adrenergic tone influences conduction properties and refractoriness of cardiac tissue,¹¹⁷ these hormone effects on the autonomic system may contribute to sex differences in the electrophysiological properties of the heart.¹¹⁸ Low levels of oestrogen and elevated levels of progesterone increase catecholamine levels, and there is higher sympathetic activity in the luteal phase of the menstrual cycle (which is characterized by low oestrogen and high progesterone levels).^{119,120} Similarly, in post-menopausal women an increased predominant sympathetic tone is associated with reduced oestrogen levels.^{36,37}



Sex differences in neuro-humoral responses

A complex nervous system controls the cardiovascular system and affects the arterial pressure, heart rate, and cardiac contractility. This neural control of the heart and vascular system is related to the sympatho-vagal balance and is regulated by vascular feedback. The renin-angiotensin system and natriuretic peptides, for example, contribute to the regulation of the cardiovascular system, partially acting as cardiac hormones.

Physiologically, women have a lower responsiveness of the mechanisms regulating arterial pressure.¹²¹ In addition, women have higher values of natriuretic peptides.¹²²

Studies evaluating sex differences in neuro-humoral control of the cardiovascular system in pathological conditions are scarce. Electrical and structural remodelling in AF does not seem to be mediated by changes in autonomic tone.¹²³ But neuro-humoral activation could be involved in differences of atrial fibrosis development via the renin-angiotensin-aldosterone system thus potentially contributing to differences in AF development.¹²⁴

Sex differences in impact of co-morbidities

Sex differences in heart failure with preserved ejection fraction and endothelial dysfunction

Heart failure with preserved ejection fraction and diastolic dysfunction are associated with a high prevalence of AF.¹²⁵ This has important implications, as AF is associated with poorer outcome in patients with HFpEF in general and women in particular.¹²⁶ Both, similar risk factors for AF and HFpEF and the haemodynamic consequences of diastolic dysfunction at the atrial level likely play a causative role.¹²⁵ Importantly, it has been shown in different populations that women have an increased age-related risk of developing diastolic dysfunction

or HFpEF as compared to men.^{126–128} At the atrial level, this is reflected by a greater atrial functional decay with age in women, as measured by longitudinal strain rate.¹²⁹ The age-related higher risk of diastolic dysfunction in women suggests a relation with oestrogen deficiency after menopause. Indeed, animal studies indicate a number of pathways, by which oestrogen deficiency can modulate diastolic dysfunction, including enhanced cardiac remodelling, LV hypertrophy and increased arterial stiffness.^{39,130,131} In a large human population study, arterial stiffness leading to diastolic dysfunction has also been shown to be greater in women.¹³² Despite the fact that hormone replacement therapy does not result in survival benefit in large studies, it does lead to improvement of diastolic function in post-menopausal women,^{133,134} which may contribute to the reduced AF incidence observed with oestrogen replacement therapy. These studies confirm the role of oestrogen deficiency in the aetiology of diastolic dysfunction and HFpEF (Table 1).

Women also have a higher rate of microvascular disease compared to men. Most of these patients with microvascular disease are in the peri-menopausal age range (45–60 years), suggesting a similar relation with oestrogen deficiency. Patients with microvascular disease are known to have a high prevalence of AF.¹³⁵ Interestingly, treatment with ranolazine, which exerts anti-anginal effects but also impacts on cardiac electrophysiology, can reduce the burden of AF in these patients.¹³⁵

Sex differences in pro-inflammatory signalling, role of epicardial fat

Several lines of evidence suggest an association between epicardial fat and AF.¹³⁶ Epicardial fat correlates with a higher prevalence of AF, a progression to atrial fibrosis and permanent AF and even a higher recurrence rate after ablation.^{137,138} Moreover, the extent of

epicardial atrial tissue is associated with lower bipolar voltage and electrogram fractionation in electro-anatomic mapping during sinus rhythm.¹³⁹ It has been demonstrated that the secretome from human epicardial adipose tissue induces myocardial fibrosis through the secretion of adipo-fibrokinases.^{140,141} Tissue fibrosis reflects a chronic inflammatory process. In fact, accumulation of fat tissue triggers a chronic low-grade activation of the innate immune system. Epicardial adipocytes are able to release pro-inflammatory adipokines and activate the chemotactic monocyte chemoattractant protein-1 (MCP-1)/C-C chemokine receptor 2 (CCR2) pathways to promote inflammatory macrophage accumulation (Figure 2). The crosstalk between adipocytes and inflammatory cells depends on the release of cytokines (IL-1, IL-6, and TNF- α) by fat tissue macrophages.¹⁴⁰ Other pro-inflammatory adipokines like leptin and resistin are also associated with incident AF in women.¹⁴² Menopausal hormonal changes are related to an increase in epicardial fat and metabolic syndrome incidence,¹⁴³ risk factors for AF development and prognosis.¹⁴⁴ Taken together, the association between increased epicardial fat and hormonal changes in post-menopausal women on one hand, as well as the causal link between epicardial fat, chronic inflammation, atrial fibrosis, and AF burden on the other hand, all point to a protective role of female sex hormones against AF development and progression (Figure 2).

Clinical implications for future therapies and research

How can we use the known mechanistic findings for future sex-specific diagnostic and therapeutic strategies?

Based on the mechanistic findings discussed above, several sex-specific therapeutic strategies might complement our current 'general' treatment approaches. In the following, we will highlight a few. As many repolarizing ion currents are lower and APD prolonged in female atria and ventricles (Sex hormone effects on electrophysiology and calcium handling section), Class III drugs further prolonging APD might be anti-arrhythmic at the atrial level at lower dosages compared to men but carry an inherent more pronounced risk of ventricular pro-arrhythmia in women even when used at low dose. Non-pulmonary triggered activity is more often found in women (Sex differences in electrophysiology and calcium handling section), suggesting that the success of AF ablation in women might be increased if other triggers apart from PV triggers are additionally tackled. As women demonstrate more pronounced AF-associated fibrotic remodelling due to an up-regulation of the TGF β /Smad3 pathway (Sex differences in atrial anatomy, structure, and function section), antifibrotic drugs (such as angiotensin receptor blockers or spironolactone) might be beneficial in women—particularly if specifically targeting this pathway. Similarly, the fact that epicardial adipocyte infiltration and consecutive pro-inflammatory signalling increase in post-menopausal women (Sex differences in pro-inflammatory signalling, role of epicardial fat section) indicates that complementing classical anti-arrhythmic therapies with anti-inflammatory treatment approaches might be beneficial in older women. Generally,

co-morbidities such as microvascular diseases or diastolic dysfunction are more often encountered in women with AF than in men (Co-morbidity-associated atrial fibrillation section/Sex differences in heart failure with preserved ejection fraction and endothelial dysfunction section), suggesting that drugs affecting these co-morbidities might be particularly efficient in women, when added to classical anti-arrhythmic therapies. As oestrogen has a beneficial/protective effect and the lack of oestrogen after menopause a harmful effect on several factors predisposing to AF (Table 1), oestrogen-based hormone replacement therapy in post-menopausal women may reduce AF incidence by reducing HFpEF and HFpEF-related AF, by impacting on electrical features and on structural remodelling and might therefore reduce AF burden in this population. However, the exact hormonal preparation might be important for anti-arrhythmic/protective effects as a reduced AF incidence has only been observed with oestradiol and oestrogen+progesterone but not with conjugated (equine) oestrogens.⁵²

What are current gaps of knowledge that we need to close to reach this aim?

As highlighted above, epidemiological and experimental evidence suggests that sex-specific differences in physiological, electrical, and structural characteristics of the atria and, particularly, in pathological remodelling of cardiac tissue in AF exist. It is still unclear, however, (i) to what extent sex differences are due to direct effects of female sex hormones, (ii) to what extent they are mediated by male sex hormone effects, or (iii) whether they mainly reflect the lack of female sex hormones in a post-menopausal population of women causatively linked to changes in co-morbidities thereby indirectly impacting on AF risk. Epidemiologic data indeed point to a direct protective role for oestrogens in this context, but mechanistic concepts are still based on observational reports and insights from animal studies. Here, more detailed mechanistic studies—ideally directly performed in human atrial tissue and cells—are warranted to increase our patho-physiological understanding and to reveal important pathways. This is mandatory to develop targeted, mechanism-based, pathway- and sex-specific therapies—either based on drugs, or on a combination of drugs with more specific ablation strategies.

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References

1. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet* 2015;**386**:154–62.
2. Heeringa J. Atrial fibrillation: is the prevalence rising? *Europace* 2010;**12**:451–2.
3. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016;**18**:1609–78.
4. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA* 1994;**271**:840–4.
5. Dagres N, Nieuwlaat R, Vardas PE, Andresen D, Levy S, Cobbe S. Gender-related differences in presentation, treatment, and outcome of patients with atrial

- fibrillation in Europe: a report from the Euro Heart Survey on Atrial Fibrillation. *J Am Coll Cardiol* 2007;**49**:572–7.
6. Volgman AS, Manankil MF, Mookherjee D, Trohman RG. Women with atrial fibrillation: greater risk, less attention. *Gend Med* 2009;**6**:419–32.
 7. Nattel S, Harada M. Atrial remodeling and atrial fibrillation: recent advances and translational perspectives. *J Am Coll Cardiol* 2014;**63**:2335–45.
 8. Linde C, Bongioni MG, Birgersdotter-Green U, Curtis AB, Deisenhofer I, Furokawa T et al. Sex differences in cardiac arrhythmia: a consensus document of the European Heart Rhythm Association, endorsed by the Heart Rhythm Society and Asia Pacific Heart Rhythm Society. *Europace* 2018;**20**: 1565–1565ao.
 9. Ball J, Carrington MJ, Wood KA, Stewart S, Investigators S. Women versus men with chronic atrial fibrillation: insights from the Standard versus Atrial Fibrillation spEcific management tudy (SAFETY). *PLoS One* 2013;**8**:e65795.
 10. Scheuermeyer FX, Mackay M, Christenson J, Grafstein E, Pourvali R, Heslop C et al. There are sex differences in the demographics and risk profiles of emergency department (ED) patients with atrial fibrillation and flutter, but no apparent differences in ED management or outcomes. *Acad Emerg Med* 2015;**22**: 1067–75.
 11. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998;**98**:946–52.
 12. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014;**129**:837–47.
 13. Ko D, Rahman F, Schnabel RB, Yin X, Benjamin EJ, Christophersen IE. Atrial fibrillation in women: epidemiology, pathophysiology, presentation, and prognosis. *Nat Rev Cardiol* 2016;**13**:321–32.
 14. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation* 2004;**110**:1042–6.
 15. Xiong Q, Proietti M, Senoo K, Lip GY. Asymptomatic versus symptomatic atrial fibrillation: a systematic review of age/gender differences and cardiovascular outcomes. *Int J Cardiol* 2015;**191**:172–7.
 16. Paquette M, Roy D, Talajic M, Newman D, Couturier A, Yang C et al. Role of gender and personality on quality-of-life impairment in intermittent atrial fibrillation. *Am J Cardiol* 2000;**86**:764–8.
 17. Ellinor PT, Yoerger DM, Ruskin JN, MacRae CA. Familial aggregation in lone atrial fibrillation. *Hum Genet* 2005;**118**:179–84.
 18. Zoller B, Ohlsson H, Sundquist J, Sundquist K. High familial risk of atrial fibrillation/flutter in multiplex families: a nationwide family study in Sweden. *J Am Heart Assoc* 2012;**2**:e003384.
 19. Chen LY, Herron KJ, Tai BC, Olson TM. Lone atrial fibrillation: influence of familial disease on gender predilection. *J Cardiovasc Electrophysiol* 2008;**19**:802–6.
 20. Oyen N, Ranthe MF, Carstensen L, Boyd HA, Olesen MS, Olesen SP et al. Familial aggregation of lone atrial fibrillation in young persons. *J Am Coll Cardiol* 2012;**60**:917–21.
 21. Karst ML, Herron KJ, Olson TM. X-linked nonsyndromic sinus node dysfunction and atrial fibrillation caused by emerin mutation. *J Cardiovasc Electrophysiol* 2008;**19**:510–5.
 22. Ravn LS, Hofman-Bang J, Diken U, Larsen SO, Jensen G, Haunso S et al. Relation of 97T polymorphism in KCNE5 to risk of atrial fibrillation. *Am J Cardiol* 2005;**96**:405–7.
 23. Mohanty S, Mohanty P, Tamaki M, Natale V, Gianni C, Trivedi C et al. Differential association of exercise intensity with risk of atrial fibrillation in men and women: evidence from a meta-analysis. *J Cardiovasc Electrophysiol* 2016;**27**: 1021–9.
 24. Drca N, Wolk A, Jensen-Urstad M, Larsson SC. Physical activity is associated with a reduced risk of atrial fibrillation in middle-aged and elderly women. *Heart* 2015;**101**:1627–30.
 25. Ofman P, Khawaja O, Rahilly-Tierney CR, Peralta A, Hoffmeister P, Reynolds MR et al. Regular physical activity and risk of atrial fibrillation: a systematic review and meta-analysis. *Circ Arrhythm Electrophysiol* 2013;**6**:252–6.
 26. Everett BM, Conen D, Buring JE, Moorthy MV, Lee IM, Albert CM. Physical activity and the risk of incident atrial fibrillation in women. *Circ Cardiovasc Qual Outcomes* 2011;**4**:321–7.
 27. Mozaffarian D, Furberg CD, Psaty BM, Siscovick D. Physical activity and incidence of atrial fibrillation in older adults: the cardiovascular health study. *Circulation* 2008;**118**:800–7.
 28. Elosua R, Arquer A, Mont L, Sambola A, Molina L, Garcia-Moran E et al. Sport practice and the risk of lone atrial fibrillation: a case-control study. *Int J Cardiol* 2006;**108**:332–7.
 29. Karjalainen J, Kujala UM, Kaprio J, Sarna S, Viitasalo M. Lone atrial fibrillation in vigorously exercising middle aged men: case-control study. *BMJ* 1998;**316**: 1784–5.
 30. Heidbuchel H, Anne W, Willems R, Adriaenssens B, Van de Werf F, Ector H. Endurance sports is a risk factor for atrial fibrillation after ablation for atrial flutter. *Int J Cardiol* 2006;**107**:67–72.
 31. Wilhelm M, Roten L, Tanner H, Wilhelm I, Schmid JP, Saner H. Gender differences of atrial and ventricular remodeling and autonomic tone in nonelite athletes. *Am J Cardiol* 2011;**108**:1489–95.
 32. Guasch E, Benito B, Qi X, Cifelli C, Naud P, Shi Y et al. Atrial fibrillation promotion by endurance exercise: demonstration and mechanistic exploration in an animal model. *J Am Coll Cardiol* 2013;**62**:68–77.
 33. Oberhauser V, Schwertfeger E, Rutz T, Beyersdorf F, Rump LC. Acetylcholine release in human heart atrium: influence of muscarinic autoreceptors, diabetes, and age. *Circulation* 2001;**103**:1638–43.
 34. Mont L, Sambola A, Brugada J, Vacca M, Marrugat J, Elosua R et al. Long-lasting sport practice and lone atrial fibrillation. *Eur Heart J* 2002;**23**:477–82.
 35. Agarwal SK, Norby FL, Whitsel EA, Soliman EZ, Chen LY, Loehr LR et al. Cardiac autonomic dysfunction and incidence of atrial fibrillation: results from 20 years follow-up. *J Am Coll Cardiol* 2017;**69**:291–9.
 36. Lavi S, Nevo O, Thaler I, Rosenfeld R, Dayan L, Hirshoren N et al. Effect of aging on the cardiovascular regulatory systems in healthy women. *Am J Physiol Regul Integr Comp Physiol* 2007;**292**:R788–93.
 37. Gautam S, Shankar N, Tandon OP, Goel N. Comparison of cardiac autonomic functions among postmenopausal women with and without hormone replacement therapy, and premenopausal women. *Indian J Physiol Pharmacol* 2011;**55**: 297–303.
 38. Bauernschmitt R, Malberg H, Wessel N, Brockmann G, Wildhirt SM, Kopp B et al. Autonomic control in patients experiencing atrial fibrillation after cardiac surgery. *Pacing Clin Electrophysiol* 2007;**30**:77–84.
 39. Magnussen C, Niiranen TJ, Ojeda FM, Gianfagna F, Blankenberg S, Njolstad I et al. Sex differences and similarities in atrial fibrillation epidemiology, risk factors, and mortality in community cohorts: results from the Biomarker Consortium (Biomarker for Cardiovascular Risk Assessment in Europe). *Circulation* 2017;**136**:1588–97.
 40. Gallagher C, Hendriks JML, Elliott AD, Wong CX, Rangnekar G, Middeldorp ME et al. Alcohol and incident atrial fibrillation—a systematic review and meta-analysis. *Int J Cardiol* 2017;**246**:46–52.
 41. Larsson SC, Drca N, Wolk A. Alcohol consumption and risk of atrial fibrillation: a prospective study and dose-response meta-analysis. *J Am Coll Cardiol* 2014;**64**: 281–9.
 42. Selmer C, Olesen JB, Hansen ML, Lindhardsen J, Olsen AM, Madsen JC et al. The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. *BMJ* 2012;**345**:e7895.
 43. Aviles RJ, Martin DO, Apperson-Hansen C, Houghtaling PL, Rautaharju P, Kronmal RA et al. Inflammation as a risk factor for atrial fibrillation. *Circulation* 2003;**108**:3006–10.
 44. Wolbrette DL. Risk of proarrhythmia with class III antiarrhythmic agents: sex-based differences and other issues. *Am J Cardiol* 2003;**91**:39d–44d.
 45. Meyer S, Brouwers FP, Voors AA, Hillege HL, de Boer RA, Gansevoort RT et al. Sex differences in new-onset heart failure. *Clin Res Cardiol* 2015;**104**: 342–50.
 46. Potpara TS, Marinkovic JM, Polovina MM, Stankovic GR, Seferovic PM, Ostojic MC et al. Gender-related differences in presentation, treatment and long-term outcome in patients with first-diagnosed atrial fibrillation and structurally normal heart: the Belgrade atrial fibrillation study. *Int J Cardiol* 2012;**161**:39–44.
 47. Rossi R, Grimaldi T, Origliani G, Fantini G, Coppi F, Modena MG. Menopause and cardiovascular risk. *Pathophysiol Haemost Thromb* 2002;**32**:325–8.
 48. Perez MV, Wang PJ, Larson JC, Virnig BA, Cochrane B, Curb JD et al. Effects of postmenopausal hormone therapy on incident atrial fibrillation: the Women's Health Initiative randomized controlled trials. *Circ Arrhythm Electrophysiol* 2012;**5**:1108–16.
 49. Bretler DM, Hansen PR, Lindhardsen J, Ahlehoff O, Andersson C, Jensen TB et al. Hormone replacement therapy and risk of new-onset atrial fibrillation after myocardial infarction—a nationwide cohort study. *PLoS One* 2012;**7**:e51580.
 50. Magnani JW, Moser CB, Murabito JM, Nelson KP, Fontes JD, Lubitz SA et al. Age of natural menopause and atrial fibrillation: the Framingham Heart Study. *Am Heart J* 2012;**163**:729–34.
 51. Tsai WC, Haung YB, Kuo HF, Tang WH, Hsu PC, Su HM et al. Hormone replacement therapy and risk of atrial fibrillation in Taiwanese menopause women: a nationwide cohort study. *Sci Rep* 2016;**6**:24132.
 52. Wong JA, Rexrode KM, Sandhu RK, Moorthy MV, Conen D, Albert CM. Menopausal age, postmenopausal hormone therapy and incident atrial fibrillation. *Heart* 2017;**103**:1954–61.
 53. Tawam M, Levine J, Mendelson M, Goldberger J, Dyer A, Kadish A. Effect of pregnancy on paroxysmal supraventricular tachycardia. *Am J Cardiol* 1993;**72**: 838–40.

54. Lee MS, Chen W, Zhang Z, Duan L, Ng A, Spencer HT et al. Atrial fibrillation and atrial flutter in pregnant women—a population-based study. *J Am Heart Assoc* 2016;**5**:e003182.
55. Salam AM, Ertekin E, van Hagen IM, Al Suwaidi J, Ruys TPE, Johnson MR et al. Atrial fibrillation or flutter during pregnancy in patients with structural heart disease: data from the ROPAC (Registry on Pregnancy and Cardiac Disease). *JACC: Clin Electrophysiol* 2015;**1**:284–92.
56. Kirbas O, Biberoglu EH, Kirbas A, Daglar HK, Kurmus O, Uygur D et al. P-wave duration changes and dispersion in preeclampsia. *Eur J Obstet Gynecol Reprod Biol* 2014;**183**:141–5.
57. Parasuraman R, Gandhi MM, Liversedge NH. Nifedipine tocolysis associated atrial fibrillation responds to DC cardioversion. *BJOG* 2006;**113**:844–5.
58. Carson MP, Fisher AJ, Scorza WE. Atrial fibrillation in pregnancy associated with oral terbutaline. *Obstet Gynecol* 2002;**100**:1096–7.
59. Ntusi NB, Badri M, Gumede F, Sliwa K, Mayosi BM. Pregnancy-associated heart failure: a comparison of clinical presentation and outcome between hypertensive heart failure of pregnancy and idiopathic peripartum cardiomyopathy. *PLoS One* 2015;**10**:e0133466.
60. Magnani JW, Moser CB, Murabito JM, Sullivan LM, Wang N, Ellinor PT et al. Association of sex hormones, aging, and atrial fibrillation in men: the Framingham Heart Study. *Circ Arrhythm Electrophysiol* 2014;**7**:307–12.
61. Lai J, Zhou D, Xia S, Shang Y, Want L, Zheng L et al. Reduced testosterone levels in males with lone atrial fibrillation. *Clin Cardiol* 2009;**32**:43–6.
62. O'Neal WT, Nazarian S, Alonso A, Heckbert SR, Vaccarino V, Soliman EZ. Sex hormones and the risk of atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis (MESA). *Endocrine* 2017;**58**:91–6.
63. Sharma R, Oni OA, Gupta K, Sharma M, Sharma R, Singh V et al. Normalization of testosterone levels after testosterone replacement therapy is associated with decreased incidence of atrial fibrillation. *J Am Heart Assoc* 2017;**6**:e004880.
64. Tsai W-C, Lee T-I, Chen Y-C, Kao Y-H, Lu Y-Y, Lin Y-K et al. Testosterone replacement increases aged pulmonary vein and left atrium arrhythmogenesis with enhanced adrenergic activity. *Int J Cardiol* 2014;**176**:110–8.
65. Tsai WC, Chen YC, Lin YK, Chen SA, Chen YJ. Sex differences in the electrophysiological characteristics of pulmonary veins and left atrium and their clinical implication in atrial fibrillation. *Circ Arrhythm Electrophysiol* 2011;**4**:550–9.
66. Tsai WC, Chen YC, Kao YH, Lu YY, Chen SA, Chen YJ. Distinctive sodium and calcium regulation associated with sex differences in atrial electrophysiology of rabbits. *Int J Cardiol* 2013;**168**:4658–66.
67. Suenari K, Hu YF, Tsao HM, Tai CT, Chiang CE, Lin YJ et al. Gender differences in the clinical characteristics and atrioventricular nodal conduction properties in patients with atrioventricular nodal reentrant tachycardia. *J Cardiovasc Electrophysiol* 2010;**21**:1114–9.
68. Takigawa M, Kuwahara T, Takahashi A, Watari Y, Okubo K, Takahashi Y et al. Differences in catheter ablation of paroxysmal atrial fibrillation between males and females. *Int J Cardiol* 2013;**168**:1984–91.
69. Goldstein J, Sites CK, Toth MJ. Progesterone stimulates cardiac muscle protein synthesis via receptor-dependent pathway. *Fertil Steril* 2004;**82**:430–6.
70. Lizotte E, Grandy SA, Tremblay A, Allen BG, Fiset C. Expression, distribution and regulation of sex steroid hormone receptors in mouse heart. *Cell Physiol Biochem* 2009;**23**:75–86.
71. Liu XK, Katchman A, Whitfield BH, Wan G, Janowski EM et al. In vivo androgen treatment shortens the QT interval and increases the densities of inward and delayed rectifier potassium currents in orchietomized male rabbits. *Cardiovasc Res* 2003;**57**:28–36.
72. Furukawa T, Kurokawa J. Non-genomic regulation of cardiac ion channels by sex hormones. *Cardiovasc Hematol Disord Drug Targets* 2008;**8**:245–51.
73. Er F, Michels G, Brandt MC, Khan I, Haase H, Eicks M et al. Impact of testosterone on cardiac L-type calcium channels and Ca²⁺ sparks: acute actions antagonize chronic effects. *Cell Calcium* 2007;**41**:467–77.
74. Odening KE. Another jigsaw piece in the complex picture of hormonal regulation of cardiac repolarization. *Eur Heart J* 2016;**37**:651–3.
75. Kurokawa J, Tamagawa M, Harada N, Honda S, Bai CX, Nakaya H et al. Acute effects of oestrogen on the guinea pig and human IKr channels and drug-induced prolongation of cardiac repolarization. *J Physiol (Lond)* 2008;**586**:2961–73.
76. Anneken L, Baumann S, Vigneault P, Biliczki P, Friedrich C, Xiao L et al. Estradiol regulates human QT-interval: acceleration of cardiac repolarization by enhanced KCNH2 membrane trafficking. *Eur Heart J* 2016;**37**:640–50.
77. Drici MD, Burklow TR, Haridasse V, Glazer RI, Woosley RL. Sex hormones prolong the QT interval and downregulate potassium channel expression in the rabbit heart. *Circulation* 1996;**94**:1471–4.
78. El Gebeily G, El Khoury N, Mathieu S, Brouillette J, Fiset C. Estrogen regulation of the transient outward K(+) current involves estrogen receptor alpha in mouse heart. *J Mol Cell Cardiol* 2015;**86**:85–94.
79. Odening KE, Choi BR, Liu GX, Hartmann K, Ziv O, Chaves L et al. Estradiol promotes sudden cardiac death in transgenic long QT type 2 rabbits while progesterone is protective. *Heart Rhythm* 2012;**9**:823–32.
80. Odening KE, Koren G. How do sex hormones modify arrhythmogenesis in long QT syndrome? Sex hormone effects on arrhythmogenic substrate and triggered activity. *Heart Rhythm* 2014;**11**:2107–15.
81. El Khoury N, Mathieu S, Marger L, Ross J, El Gebeily G, Ethier N et al. Upregulation of the hyperpolarization-activated current increases pacemaker activity of the sinoatrial node and heart rate during pregnancy in mice. *Circulation* 2013;**127**:2009–20.
82. Tang YR, Yang WW, Wang Y, Gong YY, Jiang LQ, Lin L. Estrogen regulates the expression of small-conductance Ca-activated K⁺ channels in colonic smooth muscle cells. *Digestion* 2015;**91**:187–96.
83. Hao X, Li X, Li X. 17 β -estradiol downregulated the expression of TASK-1 channels in mouse neuroblastoma N2A cells. *J Membr Biol* 2014;**247**:273–9.
84. Liang B, Soka M, Christensen AH, Olesen MS, Larsen AP, Knop FK et al. Genetic variation in the two-pore domain potassium channel, TASK-1, may contribute to an atrial substrate for arrhythmogenesis. *J Mol Cell Cardiol* 2014;**67**:69–76.
85. Qi XY, Diness JG, Brundel BJ, Zhou XB, Naud P, Wu CT et al. Role of small-conductance calcium-activated potassium channels in atrial electrophysiology and fibrillation in the dog. *Circulation* 2014;**129**:430–40.
86. Chen G, Yang X, Alber S, Shusterman V, Salama G. Regional genomic regulation of cardiac sodium-calcium exchanger by oestrogen. *J Physiol (Lond)* 2011;**589**:1061–80.
87. Yan S, Chen Y, Dong M, Song W, Belcher SM, Wang HS. Bisphenol A and 17 β -estradiol promote arrhythmia in the female heart via alteration of calcium handling. *PLoS One* 2011;**6**:e25455.
88. Tsang S, Wong SS, Wu S, Kravtsov GM, Wong TM. Testosterone-augmented contractile responses to α 1- and β 1-adrenoceptor stimulation are associated with increased activities of RyR, SERCA, and NCX in the heart. *Am J Physiol, Cell Physiol* 2009;**296**:C766–82.
89. Tsuneda T, Yamashita T, Kato T, Sekiguchi A, Sagara K, Sawada H et al. Deficiency of testosterone associates with the substrate of atrial fibrillation in the rat model. *J Cardiovasc Electrophysiol* 2009;**20**:1055–60.
90. Pfannmüller B, Boldt A, Reutemann A, Duerschmidt N, Krabbes-Graube S, Mohr F-W et al. Gender-specific remodeling in atrial fibrillation? *Thorac Cardiovasc Surg* 2013;**61**:066–73.
91. Ambrosi CM, Yamada KA, Nerbonne JM, Efimov IR. Gender differences in electrophysiological gene expression in failing and non-failing human hearts. *PLoS One* 2013;**8**:e54635.
92. Biagetti MO, Quinteiro RA. Gender differences in electrical remodeling and susceptibility to ventricular arrhythmias in rabbits with left ventricular hypertrophy. *Heart Rhythm* 2006;**3**:832–9.
93. Hudsmith LE, Petersen SE, Francis JM, Robson MD, Neubauer S. Normal human left and right ventricular and left atrial dimensions using steady state free precession magnetic resonance imaging. *J Cardiovasc Magn Reson* 2005;**7**:775–82.
94. Nikitin NP, Witte KK, Thackray SD, Goodge LJ, Clark AL, Cleland JG. Effect of age and sex on left atrial morphology and function. *Eur J Echocardiogr* 2003;**4**:36–42.
95. Maceira AM, Cosin-Sales J, Prasad SK, Pennell DJ. Characterization of left and right atrial function in healthy volunteers by cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2016;**18**:64.
96. Le Ven F, Bibeau K, De Larochelliere E, Tizon-Marcos H, Deneault-Bissonnette S, Pibarot P et al. Cardiac morphology and function reference values derived from a large subset of healthy young Caucasian adults by magnetic resonance imaging. *Eur Heart J Cardiovasc Imaging* 2016;**17**:981–90.
97. Forleo GB, Tondo C, De Luca L, Dello Russo A, Casella M, De Sanctis V et al. Gender-related differences in catheter ablation of atrial fibrillation. *Europace* 2007;**9**:613–20.
98. Cochet H, Mouries A, Nivet H, Sacher F, Derval N, Denis A et al. Age, atrial fibrillation, and structural heart disease are the main determinants of left atrial fibrosis detected by delayed-enhanced magnetic resonance imaging in a general cardiology population. *J Cardiovasc Electrophysiol* 2015;**26**:484–92.
99. Li Z, Wang Z, Yin Z, Zhang Y, Xue X, Han J et al. Gender differences in fibrosis remodeling in patients with long-standing persistent atrial fibrillation. *Oncotarget* 2017;**8**:53714–29.
100. Sanchez M, Secades L, Bordallo C, Meana C, Rubin JM, Cantabrana B et al. Role of polyamines and cAMP-dependent mechanisms on 5 α -dihydrotestosterone-elicited functional effects in isolated right atria of rat. *J Cardiovasc Pharmacol* 2009;**54**:310–8.
101. Velasco L, Sanchez M, Rubin JM, Hidalgo A, Bordallo C, Cantabrana B. Intracellular cAMP increases during the positive inotropism induced by androgens in isolated left atrium of rat. *Eur J Pharmacol* 2002;**438**:45–52.

102. Kocić I, Gruchała M, Petruszewicz J. Pretreatment of male guinea pigs by 17-beta-estradiol induces hypersensitivity of beta-adrenoceptors in electrically driven left atria. *Int J Cardiol* 2008;**129**:22–5.
103. Giraud GD, Morton MJ, Davis LE, Paul MS, Thornburg KL. Estrogen-induced left ventricular chamber enlargement in ewes. *Am J Physiol* 1993;**264**:E490–6.
104. Deng Y, Kaufman S. The influence of reproductive hormones on ANF release by rat atria. *Life Sci* 1993;**53**:689–96.
105. Frisnacho-Kiss S, Davis SE, Nyland JF, Frisnacho JA, Cihakova D, Barrett MA et al. Cutting edge: cross-regulation by TLR4 and T cell Ig mucin-3 determines sex differences in inflammatory heart disease. *J Immunol* 2007;**178**:6710–4.
106. Frisnacho-Kiss S, Nyland JF, Davis SE, Barrett MA, Gatewood SJ, Njoku DB et al. Cutting edge: t cell Ig mucin-3 reduces inflammatory heart disease by increasing CTLA-4 during innate immunity. *J Immunol* 2006;**176**:6411–5.
107. Li K, Xu W, Guo Q, Jiang Z, Wang P, Yue Y et al. Differential macrophage polarization in male and female BALB/c mice infected with coxsackievirus B3 defines susceptibility to viral myocarditis. *Circ Res* 2009;**105**:353–64.
108. Liu L, Yue Y, Xiong S. NK-derived IFN- γ /IL-4 triggers the sexually disparate polarization of macrophages in CVB3-induced myocarditis. *J Mol Cell Cardiol* 2014;**76**:15–25.
109. Akoum N, Mahnkopf C, Kholmovski EG, Brachmann J, Marrouche NF. Age and sex differences in atrial fibrosis among patients with atrial fibrillation. *Europace* 2018;**20**:1086.
110. Coumel P. Paroxysmal atrial fibrillation: a disorder of autonomic tone? *Eur Heart J* 1994;**15** Suppl A: 9–16.
111. Hirose M, Carlson MD, Laurita KR. Cellular mechanisms of vagally mediated atrial tachyarrhythmia in isolated arterially perfused canine right atria. *J Cardiovasc Electrophysiol* 2002;**13**:918–26.
112. Chen PS, Chen LS, Fishbein MC, Lin SF, Nattel S. Role of the autonomic nervous system in atrial fibrillation: pathophysiology and therapy. *Circ Res* 2014;**114**:1500–15.
113. Harvey RD, Belevych AE. Muscarinic regulation of cardiac ion channels. *Br J Pharmacol* 2003;**139**:1074–84.
114. Evans JM, Ziegler MG, Patwardhan AR, Ott JB, Kim CS, Leonelli FM et al. Gender differences in autonomic cardiovascular regulation: spectral, hormonal, and hemodynamic indexes. *J Appl Physiol* (1985) 2001;**91**:2611–8.
115. Koenig J, Thayer JF. Sex differences in healthy human heart rate variability: a meta-analysis. *Neurosci Biobehav Rev* 2016;**64**:288–310.
116. Jensen-Urstad K, Storck N, Bouvier F, Ericson M, Lindblad LE, Jensen-Urstad M. Heart rate variability in healthy subjects is related to age and gender. *Acta Physiol Scand* 1997;**160**:235–41.
117. Insulander P, Juhlin-Dannfelt A, Freyschuss U, Vallin H. Electrophysiologic effects of mental stress in healthy subjects: a comparison with epinephrine infusion. *J Electrocardiol* 2003;**36**:301–9.
118. Larsen JA, Kadish AH. Effects of gender on cardiac arrhythmias. *J Cardiovasc Electrophysiol* 1998;**9**:655–64.
119. Davidson L, Rouse IL, Vandongen R, Beilin LJ. Plasma noradrenaline and its relationship to plasma oestradiol in normal women during the menstrual cycle. *Clin Exp Pharmacol Physiol* 1985;**12**:489–93.
120. Yildirim A, Kabakci G, Akgul E, Tokgozoglu L, Oto A. Effects of menstrual cycle on cardiac autonomic innervation as assessed by heart rate variability. *Ann Noninvasive Electrocardiol* 2001;**7**:60–3.
121. Convertino VA. Gender differences in autonomic functions associated with blood pressure regulation. *Am J Physiol* 1998;**275**:R1909–20.
122. Wang TJ, Larson MG, Levy D, Leip EP, Benjamin EJ, Wilson PW et al. Impact of age and sex on plasma natriuretic peptide levels in healthy adults. *Am J Cardiol* 2002;**90**:254–8.
123. Wijffels MC, Kirchhof CJ, Dorland R, Power J, Allesie MA. Electrical remodeling due to atrial fibrillation in chronically instrumented conscious goats: roles of neurohumoral changes, ischemia, atrial stretch, and high rate of electrical activation. *Circulation* 1997;**96**:3710–20.
124. Burstein B, Nattel S. Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation. *J Am Coll Cardiol* 2008;**51**:802–9.
125. Zakeri R, Chamberlain AM, Roger VL, Redfield MM. Temporal relationship and prognostic significance of atrial fibrillation in heart failure patients with preserved ejection fraction: a community-based study. *Circulation* 2013;**128**:1085–93.
126. O'Neal WT, Sandesara P, Hammadah M, Venkatesh S, Samman-Tahhan A, Kelli HM et al. gender differences in the risk of adverse outcomes in patients with atrial fibrillation and heart failure with preserved ejection fraction. *Am J Cardiol* 2017;**119**:1785–90.
127. Ferreira RG, Nicoara A, Phillips-Bute BG, Daneshmand M, Muehlschlegel JD, Swaminathan M. Diastolic dysfunction in patients undergoing cardiac surgery: the role of gender and age-gender interaction. *J Cardiothorac Vasc Anesth* 2014;**28**:626–30.
128. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006;**355**:251–9.
129. Liao JN, Chao TF, Kuo JY, Sung KT, Tsai JP, Lo CI et al. Age, sex, and blood pressure-related influences on reference values of left atrial deformation and mechanics from a large-scale Asian population. *Circ Cardiovasc Imaging* 2017;**10**:e006077.
130. Mori T, Kai H, Kajimoto H, Koga M, Kudo H, Takayama N et al. Enhanced cardiac inflammation and fibrosis in ovariectomized hypertensive rats: a possible mechanism of diastolic dysfunction in postmenopausal women. *Hypertens Res* 2011;**34**:496–502.
131. Pedram A, Razandi M, Lubahn D, Liu J, Vannan M, Levin ER. Estrogen inhibits cardiac hypertrophy: role of estrogen receptor-beta to inhibit calcineurin. *Endocrinology* 2008;**149**:3361–9.
132. Russo C, Jin Z, Palmieri V, Homma S, Rundek T, Elkind MS et al. Arterial stiffness and wave reflection: sex differences and relationship with left ventricular diastolic function. *Hypertension* 2012;**60**:362–8.
133. Gökçe M, Karahan B, Erdöl C, Kasap H, Özdemirci S. Left ventricular diastolic function assessment by tissue Doppler echocardiography in relation to hormonal replacement therapy in postmenopausal women with diastolic dysfunction. *Am J Ther* 2003;**10**:104–11.
134. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;**288**:321–33.
135. Yuriivna Osovska N, Vitaliivna Kuzminova N. Ranolazine in treatment of stable angina in woman with atrial fibrillation and intermittent left bundle branch block—a case report. *Pol Merkuri Lekarski* 2016;**41**:287–92.
136. Gaeta M, Bandera F, Tassinari F, Capasso L, Cargnelutti M, Pelissero G et al. Is epicardial fat depot associated with atrial fibrillation? A systematic review and meta-analysis. *Europace* 2017;**19**:747–52.
137. Wong CX, Sun MT, Odutayo A, Emdin CA, Mahajan R, Lau DH et al. Associations of epicardial, abdominal, and overall adiposity with atrial fibrillation. *Circ Arrhythm Electrophysiol* 2016;**9**:e004378.
138. Canpolat U, Aytemir K, Yorgun H, Asil S, Dural M, Ozer N. the impact of echocardiographic epicardial fat thickness on outcomes of cryoballoon-based atrial fibrillation ablation. *Echocardiography* 2016;**33**:821–9.
139. Zghaib T, Ipek EG, Zahid S, Balouch MA, Misra S, Ashikaga H et al. Association of left atrial epicardial adipose tissue with electrogram bipolar voltage and fractionation: electrophysiologic substrates for atrial fibrillation. *Heart Rhythm* 2016;**13**:2333–9.
140. Baker AR, Silva NF, Quinn DW, Harte AL, Pagano D, Bonser RS et al. Human epicardial adipose tissue expresses a pathogenic profile of adipocytokines in patients with cardiovascular disease. *Cardiovasc Diabetol* 2006;**5**:1.
141. Venteclef N, Guglielmi V, Balse E, Gaborit B, Cotillard A, Atassi F et al. Human epicardial adipose tissue induces fibrosis of the atrial myocardium through the secretion of adipo-fibrocytes. *Eur Heart J* 2015;**36**:795–805a.
142. Ermakov S, Azarbal F, Stefanick ML, LaMonte MJ, Li W, Tharp KM et al. The associations of leptin, adiponectin and resistin with incident atrial fibrillation in women. *Heart* 2016;**102**:1354–62.
143. Keller KM, Howlett SE. Sex differences in the biology and pathology of the aging heart. *Can J Cardiol* 2016;**32**:1065–73.
144. Bernasocchi GB, Boon WC, Curl CL, Varna U, Pepe S, Tare M et al. Pericardial adipose and aromatase: a new translational target for aging, obesity and arrhythmogenesis? *J Mol Cell Cardiol* 2017;**111**:96–101.